Deposit Requirement

As attorney of record I hereby declare that Applicants have deposited the hybridoma (HB-12526) producing the monoclonal antibody AR47.47 with the American Type Culture Collection (ATTC), 10801 University Blvd., Manassas, VA 20110-2209, in accordance with the requirements of the Budapest Treaty, and that the deposit will be replaced if viable samples cannot be dispensed by the depository. The receipt for that deposit was included with Applicants' reply dated 4 January 2002. Applicants respectfully submit that the deposit requirement has now been met.

Enablement

Claims 14, 15, 17 and 20-21 stand rejected for non-enablement initially because Example 12, in which mice are inoculated with tumor cells prior to treatment, shows no therapeutic effect for these mice compared with controls. Applicants respectfully traverse this rejection. In the mouse model described in Example 12, the progression of tumor growth is rapid, thus not permitting the tumor cell-inoculated mice sufficient time to mount an effective immune response. In contrast, the progression of prostate cancer in humans is slow, and thus more likely to allow an effective host immune response to develop. Applicants thus respectfully submit that Example 11, in which pre-administration of MAb AR47.47 allows sufficient time for an effective immune response to develop, more closely mimics the human prostate cancer situation. In Example 11, there is a clear difference between the MAB AR47.47 treated mice and the control mice. Thus, if Example 11 more closely resembles the human condition, one skilled in the art would predict that the treatment of humans suffering from prostate cancer would be effective.

New claims 28-34 are rejected on a similar basis, however, Applicants note that claims 28-34 do not recite a therapeutic benefit, and are therefore fully supported by Examples 5-8. Such experiments are useful in determining the effects of varying levels of circulating PSA on e.g., precancerous patients.

At the interview, the Examiner indicated that evidence that Ab2 and/or Ab3 would be produced under the conditions of Example 12 would be favorably considered. Despite some false positive control experiment, Applicants note that positive results for Ab2 were obtained in experiments 10 and 14 (see page 38 at line 10) and that both Ab2 and Ab3 were obtained in experiments 10 and 14 (see page 39 at top of page). Accordingly, although there were imperfections in the experiments, at least in some cases Ab2 and/or Ab3 were produced upon administration of AR47.47, but not when control Ab was used.

Although unclear, it appears that all of the claims are rejected for non-enablement due to T-cell anergy in the presence of a tumor burden. For the reasons cited in the preceding paragraph applicants respectfully assert that this rejection should be limited to claims 14, 15, 17 and 20-21.

This rejection relies primarily upon the reference by Sherman *et al.* However, this reference ends optimistically for approaches such as the presently claimed invention. In its final paragraph, Sherman *et al.* states "These experiments suggest that even in situations where tolerance to a self antigen has been established, it may be possible to activate the residual T-cell repertoire to the extent necessary to prevent tumor cell growth." Sherman *et al.* concludes "Because it is generally the case that tumor-associated antigens are expressed at a higher level than normal tissue, these results encourage the prospect of eliminating tumor without induction of autoimmunity." This is certainly the case for prostate cancer. Thus, Applicants respectfully submit that Sherman *et al.* actually supports the likelihood of success of the presently claimed invention.

Moreover, the specification describes a mechanism by which such T-cell anergy may be averted. At page 14, lines 15-17, the specification states that "The second mechanism of action involves cellular immunity – the administered anti-PSA antibody binds to circulating PSA to form a complex suitable for binding antigen presenting cells (APCs). Of particular interest, this mechanism of action generates a multi-epitopic immune response against the PSA." Thus, the presentation of the antibody-PSA complex

may lead to presentation of cryptic epitopes to which anergy has not been established. The specification goes on to describe the potential importance of dendritic cells to this mechanism. Further support for this mechanism is found in a recently published paper by Berlyn *et al.*, presented herewith, in which a combination of PSA, dendritic cells and MAb 47.47 leads to an immune response against two unrelated PSA peptides, but not an unrelated HIV-derived peptide (see page 280, 2d column, first paragraph). Applicants respectfully submit that these findings, taken together rebut the suggestion that T-cell anergy is likely to interfere with the success of the claimed invention.

All claims are also rejected based on the scope of the "binding agent". However, if the above-discussed mechanism is active, as it appears to be, then the nature of the target sequence, and not the binding agent should be important. It appears that the present inventors have surprisingly discovered a target which, when bound, leads to presentation of the binding agent-PSA complex in a manner leading to a multi-epitopic response. Accordingly, Applicants respectfully submit that the scope of the present claims is appropriate.

Novelty

All claims are presently rejected as anticipated by Giri *et al.*, on the basis that the polyclonal antibodies of that reference would inherently include binding agents to Applicants' claimed target. However, to anticipate a patent claim, the inherency of the element in the reference corresponding to the limitation in the claim must be clear. Given the diversity of possible antibodies to various targets on an antigen it is anything but clear that the polyclonal antibodies of Giri *et al.* would include a binding agent to Applicants claimed target. As further evidence of this fact, Applicants provide herewith a copy of the ISOBM TD-3 International Workshop on Monoclonal Antibodies against PSA. Of 83 monoclonal antibodies tested, none of them bound to the epitope comprising amino acid sequences 139-163. Accordingly, this rejection should be withdrawn.

For the reasons discussed above, Applicants respectfully submit that claims 14, 15, 17, 20-21 and 28-34 are now ready for allowance. If the Examiner believes that any

discussion of this reply would be helpful, the Examiner is invited to call the undersigned attorney by telephone at 781-938-1805.

Respectfully submitted,

Date: 15 August 2002

Wayne A. Keown, Ph.D.
Reg. No. 33,923

KEOWN & ASSOCIATES
500 West Cummings Park
Suite 1200
Woburn, MA 01801
781-938-1805 (Telephone)
781-938-4777 (Facsimile)